

# *The Role of Mucosal Immunity in the Pathogenesis of IgA Nephropathy and the Progress of Chinese Medicine Research*

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**Abstract:** IgA nephropathy (IgAN) is one of the most common pathological types of primary glomerular disease in Asian countries and an important cause of end-stage renal disease. The pathogenesis of IgA nephropathy is still unclear and no specific treatment is available. Recent relevant studies have shown that mucosal immunity is closely related to the pathogenesis of IgA nephropathy, therefore, this article describes the pathogenesis of IgA nephropathy, focusing on the recent progress of mucosal immunity in the pathogenesis of IgA nephropathy.

## 1. Introduction

IgA nephropathy (IgAN) is a common primary glomerular disease, also considered as an immune-mediated disease, which mainly manifests as asymptomatic hematuria, may be accompanied by varying degrees of proteinuria, hypertension and impaired renal function, and is one of the common diseases leading to end-stage renal disease. The pathogenesis of IgAN is still unclear, but there is a consensus that IgA immune complexes are deposited abnormally in the glomerular thylakoid region, and this IgA molecule is produced when foreign pathogenic bacteria damage the mucosal barrier, which induces specific B- and T-cell immune responses, leading to a relative or absolute increase in the production of helper T-cells<sup>2</sup> (Th<sub>2</sub>), and induces abnormal Ig A1 glycosylation abnormality, which eventually leads to elevated galactose-deficient Ig A1 (Gd-Ig A1) levels and causes disease[1]. Therefore, more clinical studies have suggested that the mucosal immune system (MIS) plays an important role in the pathogenesis of IgAN, and the MIS is widely distributed in the lymphoid tissues of the respiratory, gastrointestinal, and genitourinary tracts, as well as in some exocrine glands, which are the main sites where the body performs local specific immune functions[2]. In this paper, we review the correlation between mucosal immunity and IgAN, as it has been shown that abnormal mucosal immune responses can lead to the development or exacerbation of IgAN.

## 2. Respiratory mucosal immunity and IgAN

Tomino first proposed the relationship between the tonsils and IgAN in 1983, and the tonsils, as the first defense organ of the oropharynx, are the predominant immunologically active tissue in the upper respiratory tract, playing a role in both systemic and local mucosal immunity against various antigens that invade the mucosal epithelial surface as well as immunologically active cells including T and B lymphocytes[3]. Clinically, some patients with IgAN have been found to have exacerbated clinical symptoms in close association with upper respiratory tract infections, often with changes in apparent carnivorous hematuria within hours to two days after mucosal infection, and the B-cell response after mucosal infection, especially tonsillitis, may produce this nephritogenic IgA1 molecule[3]. Haemophilus parainfluenzae is one of the common bacteria found in tonsils, and antigens and antibodies to this bacterium have been reported to be found in glomerular thylakoids and serum of IgAN patients, suggesting that Haemophilus parainfluenzae infection may be involved in the pathogenesis of IgAN[4]. Amove et al [5] found that in mice defective in the induction of mucosal immune tolerance, transnasal administration of Sendai virus, a common respiratory tract infection pathogen, was found to cause microscopic hematuria with persistent IgA deposition in the thylakoid region. Therefore, in terms of treatment, many studies have concluded that tonsillectomy has a positive impact on the improvement of renal function and prognosis in patients with IgAN. A Chinese single-center clinical study also found an increased frequency of memory B cells in the blood and tonsils of IgAN patients, and these frequencies were significantly reduced after tonsillectomy. Also, we found in our clinical practice that microscopic hematuria was greatly improved by actively preventing the occurrence of upper respiratory tract infections and avoiding repeated irritation of the mucosa.

## 3. Intestinal mucosal immunity and IgAN

Previous studies have largely established that the respiratory mucosa has a great relationship with the development of IgAN, while the influence of intestinal mucosal immunity on IgAN has been recently proposed. Abnormalities in intestinal mucosal immunity are associated with many factors, such as food antigens, dysbiosis of the intestinal flora, and genetic and environmental differences.

The human intestinal tract is home to trillions of microorganisms, each attached to different parts of the intestine and playing different roles, forming a stable and beneficial dynamic balance with the body that plays an important role in maintaining immune homeostasis and protecting against foreign pathogens. When the immune function of the intestinal mucosa is dysregulated, the body has a defective immune tolerance to intestinal flora, the barrier function of intestinal mucosa decreases, and toxins are absorbed into the blood, activating mucosa-associated lymphoid tissue (MALT), producing a large amount of abnormal glycosylated Ig A1 and forming circulating immune complexes, which are eventually deposited in the glomerular The thylakoid region and lead to Ig AN[6].

It has been suggested that the release of intestinal microbiota such as lipopolysaccharide (LPS) and lipo-lactic acid can activate the gut-associated lymphoid tissue (GALT) through the TLR pathway[7], and under normal conditions, the intestinal microbiota can promote the repair of intestinal mucosal damage through TLRs signaling, and when the intestinal flora is dysregulated and the intestinal barrier is altered, the patient's intestinal permeability increases and LPS is absorbed into the blood. Bacterial LPS can activate TRL4 on the surface of lymphocytes, induce Cosmic molecular chaperone methylation, reduce galactosyltransferase activity, and lead to abnormal glycosylation of Ig A1[8].

Food antigens can act as exogenous antigens to stimulate macrophages to secrete cytokines such

as IL-1 and promote B cell proliferation and differentiation to produce excess IgA[9]. It has been reported in the literature that the level of specific antibodies to common food allergens is significantly elevated in IgAN patients and is proportional to the deposition of IgA immune complexes[10], whereas a decrease in serum IgA levels and varying degrees of decrease in hematuria and proteinuria have been detected in patients with IgAN after administration of gluten-free foods[11].

In genome-wide association studies, investigators determined the relationship between the genetic probability of IgAN and climate, pathogen load and diet, however, the strongest positive correlation was shown between the diversity of local pathogens (including viruses, bacteria, protozoa and helminths) and the genetic risk score for IgAN[12]. The increased prevalence of IgAN in some regions may be the result of defensive adaptation to mucosal invasion by intestinal helminths. On the other hand, IgAN susceptibility genes are associated with susceptibility to inflammatory bowel disease (IBD) and their proteins are associated with mucosal immune responses that protect intestinal integrity and control the intestinal environment, especially since these genetic risk alleles greatly influence the age of disease onset[7]. The involvement of these genetic alleles provides a rationale for the important role of mucosal immune response in IgAN and opens up new ideas for our subsequent study of treatment options for IgAN.

#### **4. Chinese medicine's understanding of the immune mechanism of IgAN mucosa**

IgA nephropathy does not have a specific Chinese medical name in ancient texts, but is mostly classified as "hematuria", "lumbago", "kidney wind", "deficiency labor". The core pathogenesis of the disease is the deficiency of the right and the evil, and it is also related to external influenza, damp-heat, blood stasis and other etiologies. Clinically, the acute attack of IgAN is dominated by evil, mostly related to external wind-heat, "Ling Shu - meridians" cloud: "kidney foot Shao Yin pulse ..... into the lungs, following the throat, holding the tongue this ..... is the main kidney by the sick, The mouth is hot and the tongue is dry, the throat is swollen with upper gas, the quarrel is dry and painful[13], and IgAN mostly develops after a series of factors related to mucosal immunity such as upper respiratory tract infections, tonsillitis, urinary tract infections, etc. Therefore, the following also discusses the understanding of mucosal immune mechanisms in Chinese medicine.

##### **4.1. Theory of Wei Qi**

Some scholars have described the influence of mucosal immunity on IgAN from the aspect of Chinese medicine, which can be firstly developed from the theory of Wei Qi, which in Chinese medicine has the role of protecting the muscle surface and defending against external evil, and the strength of Wei Qi can reflect the ability of the body to resist the invasion of external evil. Zhou Donghao et al [14] summarized the description of the defensive role of Wei Qi in the Emperor's Internal Canon and concluded that Wei Qi has characteristics of latency, easy excitation, induction of disease and evil, and tending to disease in operation, which are very similar to the description of the recognition, capture, proliferation and activation of pathogens by immune cells in modern immunology, as well as the effective process and the tending to disease aggregation characteristics of immune cells such as white blood cells. Secretory IgA is an antibody specific to the mucosal surface, which is synthesized and secreted mainly in the respiratory and intestinal tracts and plays a role in preventing the attachment and invasion of pathogens to the epithelial layer[15], and this is similar to the role of Wei Qi in warding off external evil. In the "Medical Principles of Xuyu", it is mentioned that Wei Qi "protects the surrounding body ..... from external evil"[16]. Therefore, only when the Wei Qi is strong enough to resist the invasion of external evil can the organism flourish, as mentioned in Huang Di Nei Jing Su Wen (Yellow Emperor's Classic of Internal Medicine):

"When the righteous Qi exists within, evil cannot be destroyed" and "Where evil comes together, its Qi will be deficient. The qi will be deficient".

## 4.2. Theory of pharynx

The Chinese medical theory is that the throat is the gateway to the lung and the main body of the kidney, and the lung and kidney meridians are connected, gold and water are mutually influencing each other, and the throat is connected to the kidney through the lung system; IgAN patients with acute onset of swelling and pain in the throat are mostly injured by external evil invasion of the lung guard, and the throat is the first gateway to the lung, and external evil is injured to the kidney through the throat and down the meridian. As mentioned in the *Ulterior Medical Dictionary*, "all sore throats are the disease of Shao Yin", and the throat is dry and painful when it is not moistened by the kidney essence; the *Yellow Emperor's Classic of Internal Medicine* also points out that "when the wind evil enters Shao Yin, it will urinate blood", and the evil of external wind-heat enters the kidney meridian through the meridian, and when the kidney loses its seal, it can be seen as The hematuria can be seen when the external wind-heat evil enters the kidney meridian through the meridian and the kidney is not sealed[17]. In modern medicine, "tonsils" can be classified as "pharynx" in Chinese medicine. After infection by pathogens, B cells distributed on the mucosal surface of tonsils are activated by the stimulation of antigens, which leads to excessive secretion of IgA1 and eventually to the development of the disease. This leads to the development of the disease.

## 4.3. Damp heat theory

The meaning of dampness and heat in Chinese medicine covers a wide range of pathogenic factors, which is a combination of dampness and heat. Dampness is a yin evil, easily injuring yang energy, and dampness is sticky and heavy, easily blocking the qi mechanism; heat is a yang evil, easily consuming qi and injuring fluid, generating wind and moving blood, and dampness and heat evaporate each other, damaging the body and causing the disease to linger. Many scholars in continuous research also found that damp-heat blockage is one of the pathogenesis of IgAN, but also an important cause of recurrent attacks and progression of the disease, Ig A nephropathy patients produce damp-heat mainly due to the following factors: First, the patient's body is deficient in positive energy, external evil, wind-heat evil poison invasion, damp-heat combined, resulting in the Sanjiao Qi-transformation malfunction, water-damp internal stagnation, depression and heat, and see damp-heat; Second, patients taking long-term The second is that the patient takes hormones or some kidney stimulant drugs for a long period of time, which help Yang to turn heat and combine with internal dampness to form damp-heat; the third is that the patient is overworked and tired, in addition to a poor diet, which damages the spleen qi, and the spleen qi deficiency hurts the kidney qi, and water dampness is generated internally, which turns into heat after a long period of time, resulting in damp-heat[18]. According to Prof. Liu Baohou, the infection in modern medicine is the same as the pathogenesis of damp-heat in Chinese medicine, but the theoretical understanding of Chinese and Western medicine is different[19], and he also put forward the view that "if damp-heat is not removed, protein is difficult to be eliminated". Based on this theory, we also found that the exacerbation or recurrence of IgAN mostly occurs in abnormal mucosal immune responses such as upper respiratory infections, gastrointestinal infections, and urinary tract infections, and the symptoms of the three jiao, such as redness and swelling of the throat, dry mouth and inability to drink, drowsiness of the limbs, yellow urine or frequent and painful urination, which are caused by the evil of damp-heat as proposed in traditional medicine, are closely related to the infection as mentioned in modern medicine. Therefore, if a patient clinically exhibits symptoms related to damp-heat evidence, we can consider the presence of infectious lesions in the organism to start with,

especially from a mucosal immune-related perspective to find the etiology.

## **5. Chinese medicine treatment based on mucosal immune mechanism**

### **5.1. Treatment from the lung**

The lung is a delicate organ, which is easily attacked by external evil through the skin or nasal orifices. According to the law of transmission of the twelve meridians, the kidney meridian travels in and out of the lung, and diseases of the lung meridian can be inflicted on the kidney and cause the same disease in the lung and kidney. At the same time, some studies have also confirmed that the mucosal immune mechanism in IgAN patients with deficient body surface, deficiency of lung qi, and external wind-heat evil toxins is similar to that in modern medical theory[20]. Based on the above theory, we can conclude that benefiting the lung to consolidate the surface, clearing heat and detoxifying the toxin is the main treatment rule, and Yu Ping Feng San is selected as the main formula, accompanied by clearing heat and detoxifying the toxin, diuresis and dampness or activating blood circulation and resolving blood stasis. Some scholars have formulated their formula of Yi Qi Qing Jie (composed of raw Astragalus, Atractylodes, Fructus, Jinyin Hua, and Forsythia), and found through clinical observation that this formula can improve the patient's TCM syndrome score and reduce the urine protein level[21]. Based on the "one lung-kidney concept", Professor Zhou Zhongying concluded that the five methods of draining wind and promoting lung, benefiting qi and warming yang to promote water retention, clearing lung and detoxifying toxins, smooth qi and promoting water retention, and nourishing yin to nourish the lung can effectively delay the progression of kidney function while improving clinical symptoms[22].

### **5.2. Treatment from the pharynx**

Therefore, we can follow this theory in the treatment of IgAN patients with recurrent throat redness, swelling, pain, dryness and itching as the first symptom to adopt the treatment of "nourishing Yin, clearing heat, and sharpening the throat. Therefore, we can follow this theory and adopt the treatment of "nourishing yin, clearing heat, and promoting pharynx" for IgAN patients with recurrent red, swollen, painful, and dry throat as the first symptoms. According to the theory of "treating from the pharynx", Li Siping [23] formulated a compound formula of Chinese herbs (Yinhua, Forsythia, Cicada, Radix et Rhizoma, Scutellariae, Radix Scutellariae, Radix et Rhizoma, Rhizoma, Rhizoma and Rhizoma) with the effect of clearing heat and detoxifying and dispersing wind and evil spirits, and the results showed that the symptoms of sore throat and hematuria in the observation group were significantly reduced after treatment, and the adverse effects were lower than those in the control group. Wang Jiming[24], who used the treatment principle of clearing heat and promoting pharynx, strengthening the spleen and tonifying the kidneys, achieved great efficacy with the self-prepared compound Jianrenkang, which improved the patients' pharyngitis, hematuria, and proteinuria, and the total effective rate of the treatment group reached 88.33%. Du Anmin [25] treated IgAN from pharyngeal theory, and the results showed that the patients' 24-h urine protein quantification, urine red blood cell count and blood creatinine were improved. Wang Xinhui et al [26] found that the combination of Yiqi nourishing Yin and pharyngeal formula with pharyngeal pecking treatment could reduce proteinuria and hematuria in patients with IgAN with pharyngeal inflammation. From the above examples of clinical observations, we can see that treating the kidney from the pharynx can greatly improve the clinical symptoms of patients and delay the progression of the disease.

### 5.3. Treatment from the intestine

The theory of the "intestine-kidney axis" in Chinese medicine is an important guide in the treatment of IgAN. The Suwen - Five Organs, "The Five Tibetan Turbid Qi, called the House of Transfusion, which can not stay for long, the transmission of diarrhea." The intestines and kidneys are in the same lower jiao, the real is the drainage, through the internal organs to drain the turbidity, from the lower diarrhea, which can take advantage of the situation, so that the evil has a way out. The method of draining turbidity from the internal organs can strengthen the function of transferring and transforming the large intestine, dispel the evil toxins in the body, and adjust the qi of the internal organs to protect the barrier function of the intestinal mucosa from being damaged, to achieve the purpose of delaying the disease. Some studies have found that exerting the laxative effect of Da Cheng Qi Tang can reduce the absorption of endotoxins as well as inflammatory factors in intestinal tissues, promote gastrointestinal peristalsis, regulate intestinal flora, and protect the intestinal barrier function[27]. Chang Qintao et al [28] found that reserved enemas with Yi kidney soup could effectively remove toxins and improve the microinflammatory state of patients. In conclusion, under the condition of sufficient positive energy in the early stage of the disease, we can use the method of clearing the internal organs and draining turbidity to eliminate external evil and remove toxins based on the theory of gastrointestinal "to pass for use", and finally maintain the balance of intestinal microecology effectively.

### 6. Conclusions and Outlook

Through various studies, we found that mucosal immune mechanisms play an important role in the pathogenesis of IgAN, and both respiratory mucosal immunity and gastrointestinal mucosal immunity can improve the prognosis of IgAN to varying degrees. The etiology, clinical manifestations, and treatment of IgAN in TCM correspond to the mucosal immune mechanisms discussed in modern medicine, and the use of TCM treatment has become a new direction to improve the outcome of IgAN. Therefore, a focus of future research could be to combine the physical factors of TCM with mucosal immunity, to prevent the recurrence or exacerbation of the disease by applying the idea of treating the disease before it occurs, and to conduct multicenter studies to treat IgAN from different perspectives.

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